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Homozygosity Mapping in a Family With Microcephaly, Mental Retardation, and Short Stature to a Cohen Syndrome Region on 8q21.3 - 8q22.1: Redefining a Clinical Entity

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A syndrome of microcephaly, progressive postnatal growth deficiency, and mental retardation was observed in two brothers and their cousin from a multiply consanguineous kindred of Lebanese descent. Hypotonia, chorioretinal dystrophy, and myopia were also identified. The severity of the condition varied among the closely related patients. Because of absence of a distinctive facial appearance, the degree of mental retardation, and short stature, the initially considered clinical diagnosis of Cohen syndrome was withdrawn and a novel genetic entity was assumed. Homozygosity mapping in this family assigned the gene to a 26.8-cM region on the chromosome band 8q21.3 -22.1, between the microsatellites at D8S270 and D8S514. The maximum two-point LOD score was found for marker at D8S267 (Z_{max}=3.237 at O_{max}=0.00). Intriguingly enough, the identified gene region overlaps the refined gene region for Cohen syndrome (COH1) [Kolehmainen et al., 1997: Euro J Hum Genet 5:206–213]. This fact encourages the hypothesis that the described kindred segregates for a variant of Cohen syndrome and suggests a redefinition of its phenotype. Am. J. Med. Genet. 92:285–292, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS: Mirhosseini-Holmes-Walton syndrome; hypotonia; chorioretinal dystrophy; heterogeneity

INTRODUCTION

Microcephaly, mental retardation, short stature, and hypotonia occur in many different mendelian and aneuploidy syndromes. Cohen and Mirhosseini-Holmes-Walton syndromes are among several autosomal recessive genetic conditions comprising these clinical characteristics.

Cohen syndrome [Cohen, 1973] initially was characterized by obesity, mental retardation, hypotonia, narrow hands and feet, and by a distinctive craniofacial appearance with prominent upper central incisors. The later definition of Cohen syndrome by Escobar [1990] requires the presence of at least five of the following major manifestations: obesity, short stature, mental retardation, hypotonia, maxillary hypoplasia, short philtrum, micrognathia, narrow hands and feet, and high-arched palate. Nevertheless, according to several case reports, the individual findings of Cohen syndrome are not specific and their variability is great [Fryns et al., 1996]. In some cases this allows false diagnosis of an otherwise distinct syndrome [Gorlin et al., 1990]. Nevertheless, in Finnish patients a clinically homogeneous phenotype of Cohen syndrome was described with additional ophthalmological findings and marked neutropenia [Kivitie-Kallio et al., 1999; Norio et al., 1984]. Linkage studies have localized the gene in Finnish patients to a 10-cM region at 8q21.3, and linkage disequilibrium investigations have narrowed the candidate gene region to the immediate vicinity of marker D8S1762 [Kolehmainen et al., 1997]. No gene has been reported so far.

Mirhosseini-Holmes-Walton syndrome [Mirhosseini et al., 1972] is very rare and was first described in two sibs with microcephaly, retinal pigmentary degeneration, and severe mental retardation. Clinical presentation in most reported patients with Mirhosseini-Holmes-Walton syndrome overlaps the phenotype seen

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in Cohen syndrome patients. Therefore, it has been suggested that both conditions represent a single entity [Norio and Raitta, 1986]. Nevertheless, no linkage data have been published in this syndrome and it remains unknown whether these conditions are allelic.

We report here on three closely related patients with postnatal microcephaly, progressive growth delay, mental retardation, and variable overlap with the Cohen and Mirhosseini-Holmes-Walton syndromes. The severity of clinical findings varied considerably among these patients. Based on the pedigree and the existence of multiple consanguinity an autosomal recessive inheritance was assumed. Possible chromosomal and metabolic disorders were excluded. Subsequently, a whole genome search for linkage was performed and the locus for this syndrome was assigned to 8q21.3-22.1. The identified region overlaps the already published one of Cohen syndrome [Kolehmainen et al., 1997].

CLINICAL REPORTS

The Lebanese family is multiply consanguineous and the affected patients were offspring of first cousin parents (Fig. 1). The further family history was unremarkable.

Patient 1

The affected propositus was seen at age 17 years for severe mental retardation and lack of speech. He was born at term after a normal pregnancy; length was 50 cm. There were no feeding or respiratory problems during infancy. Bilateral congenital clubfoot was repaired at 7 years, and afterwards he managed to walk short distances unaided. The patient was unable to feed himself and had no sphincter control. Autistic symptoms with stereotypic hand movements became apparent early in childhood.

His height was 148 cm (−4.2 SD) and he had a weight of 32 kg (3rd centile for this age is 49 kg, 3rd centile for height is 30.1 kg), and a head circumference (OFC) of 49.5 cm (−4.8 SD) (Fig. 2a). He had everted lips, downslanting palpebral fissures, synophrys (present in all unaffected relatives) (Fig. 2b), marked hypotonia, inadequate muscle development, generalized joint laxity, widely spaced nipples, and narrow hands and feet. Sexual development corresponded to age.

Ophthalmologic examination documented strabis-

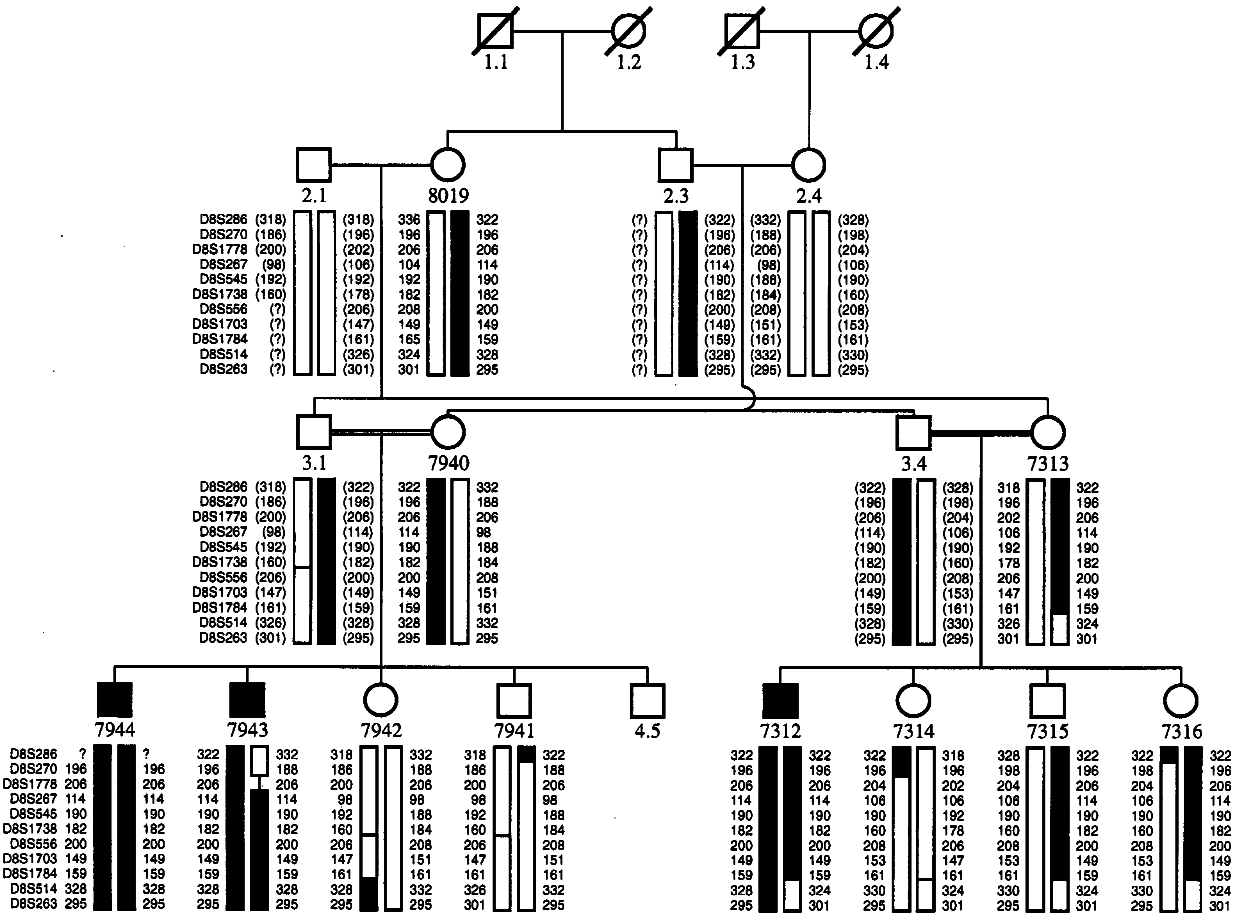

Fig. 1. The pedigree and haplotype study of the affected family. Arabic numbers denote subjects investigated in this linkage study. Black bar represents affected haplotype; horizontal lines in open boxes indicate a recombination event in the unaffected haplotype.

mus divergens, myopia (–2D), astigmatism, slow pupillary reactions, constriction of retinal vessels, pale papillae, and apparent tapetoretinal degeneration. Pigment deposits of the so-called bone spicule type were not seen. Visual fields, color vision, and electroretinography (ERG) could not be tested due to severe mental retardation.

Patient 2

The term delivery of the younger brother of patient 1 was uncomplicated; his weight was 2500 g and length 51 cm. He was floppy, and his early development was delayed. He was able to stand without support at 4 years. He began walking at 5 years. Stereotypical behavior was noted during childhood. He could not speak and had extremely limited comprehension. He has not achieved bowel or bladder control.

Anthropological examination at 9.5 years showed height of 115 cm (–3.6 SD), weight of 24.2 kg (–1.0 SD), OFC of 49 cm (–3.0 SD), synophrys, mild truncal obesity, narrow hands and feet, and mild joint hyperextensibility. No neurological abnormalities were present except for muscular hypotonia. Tapetoretinal pigment degeneration was suspected on ophthalmological examination. Pupillary reflexes were symmetrically present, strabismus was absent. Repeated hematological examinations demonstrated low white blood cell count (4.7–5.7 10^9/L) but no neutropenia (58–60% neutrophils).

Patient 3

The cousin of patients 1 and 2 was born at 36 weeks of gestation after an uneventful pregnancy, with a weight of 2300 g, length of 46 cm, and OFC of 32.5 cm. The infant had Apgar scores of 10 and 10. No medical problems were noted in the first 9 months of life. Due to persistent muscular hypotonia, physiotherapy was initiated.

Diagnostic evaluation at 11 months demonstrated a developmental level between 3 and 5 months. The growth curve of the first year of life showed progressive microcephaly with OFC of 41.4 cm at the chronological age of 9 months (–3.4 SD, corrected age of 8 months) and an OFC of 42.5 cm at 12 months (–3.6 SD, corrected age of 11 months). Postnatal growth was retarded, with a height of 70 cm at 12 months (–2.5 SD for corrected age of 11 months). Psychomotor development was delayed: the patient sat at 15 months, walked at 24 months, and used a few words at 30 months. He had no bowel and bladder control.

Examination at 4 years showed a height of 96.5 cm (–2.0 SD), weight of 17.8 kg (0.4 SD), and an OFC of 46.5 cm (–3.6 SD) (Fig. 2c). He had synophrys, simple philtrum, small mouth, thin upper lip (Fig. 2d), mild obesity, hypoplastic and inverted nipples, joint laxity, wide gap between hallux and second toe, and shawl scrotum. The fingers appeared elongated. White blood cell count was normal.

At 6 years his height was 104 cm (–2.8 SD), weight 19.8 kg (0.7 SD), and OFC 47 cm (–3.9 SD); he had high-grade myopia (–8D), astigmatism, and intermittent divergent strabismus. Diffuse pigmentary deposits without bone spicules in the periphery were observed in both fundi, and a bull's eye pattern was described in the maculae.

HOMOZYGOSITY MAPPING IN THE AFFECTED INDIVIDUALS

Subjects and Methods

Linkage analysis was performed on 11 individuals from three generations of this multiply consanguineous family (Fig. 1); involved relatives agreed to cooperate, and their blood was drawn with informed consent.

DNA was extracted by use of the Nucleon II Kit (Scotlab, Lanarkshire, U.K.), according to the manufacturer's instructions. Analyzed microsatellite markers belong to the MDC-Généthon microsatellite-mapping panels based on the Généthon final linkage map [Dib et al., 1996]. The markers are evenly distributed over the entire genome with an average distance of 11 cM. Markers were amplified individually in a final reaction volume of 10 μL containing 10 mM Tris, 1.5 mM $MgCl_2$, 100 μM each dNTP, 0.4 U polymerase (Perkin-Elmer Biosystems, Weiterstadt, Germany), 7.0 pmol of each primer, and 25 ng of genomic DNA. One of the primers was end-labeled with fluorescent dye. DNA amplification was carried out in an MJ Research PTC-225 thermal cycler. Polymerase chain reactions were then pooled and electrophoresed on an ABI 377 automatic sequencer. Data were analyzed using the Genescan v2.1 software and Genotyper v2.0 software (Perkin Elmer).

Linkage Analysis

Two-point LOD score calculations were performed with the LINKAGE v5.2 program package [Lathrop and Lalouel, 1984] with the help of the newly developed LINKRUN computer program [Wienker, unpublished data], using an autosomal recessive model. Most likely haplotypes were constructed either manually or with CRI-MAP v2.41 option Chrompic [Lander and Green, 1987].

The genetic maps and marker data were obtained from the 1996 Généthon map [Dib et al., 1996] and from NCBI Human Gene Map 99 [Deloukas et al., 1998]. The search for candidate genes in the chromosome 8q21.3 region was performed by comparative analysis of the human EST sequence data with help of the program BLAST and the NCBI UniGene collection.

Results of Linkage Analysis

Homozygosity mapping was performed with 382 polymorphic loci; the marker D8S545 was the only one with a significantly positive LOD score. To determine the size of the disease gene region, further microsatellite markers localized within this area were characterized. The construction of likely haplotypes identified a key recombination event in individual 7943 at D8S270 and in individual 7312 at the locus D8S514; this determined a 26.8-cM gene region on 8q21.3-22.1 between the flanking markers D8S270 and D8S514 (Fig. 1, 3). The recombination status of the locus D8S1778 in individual 7943 could not be established due to its homozygosity in person 7940, the mother of this patient (Fig. 1). The markers at D8S1778, D8S267, D8S1738, D8S556, D8S1703, and D8S17 cosegregated with the

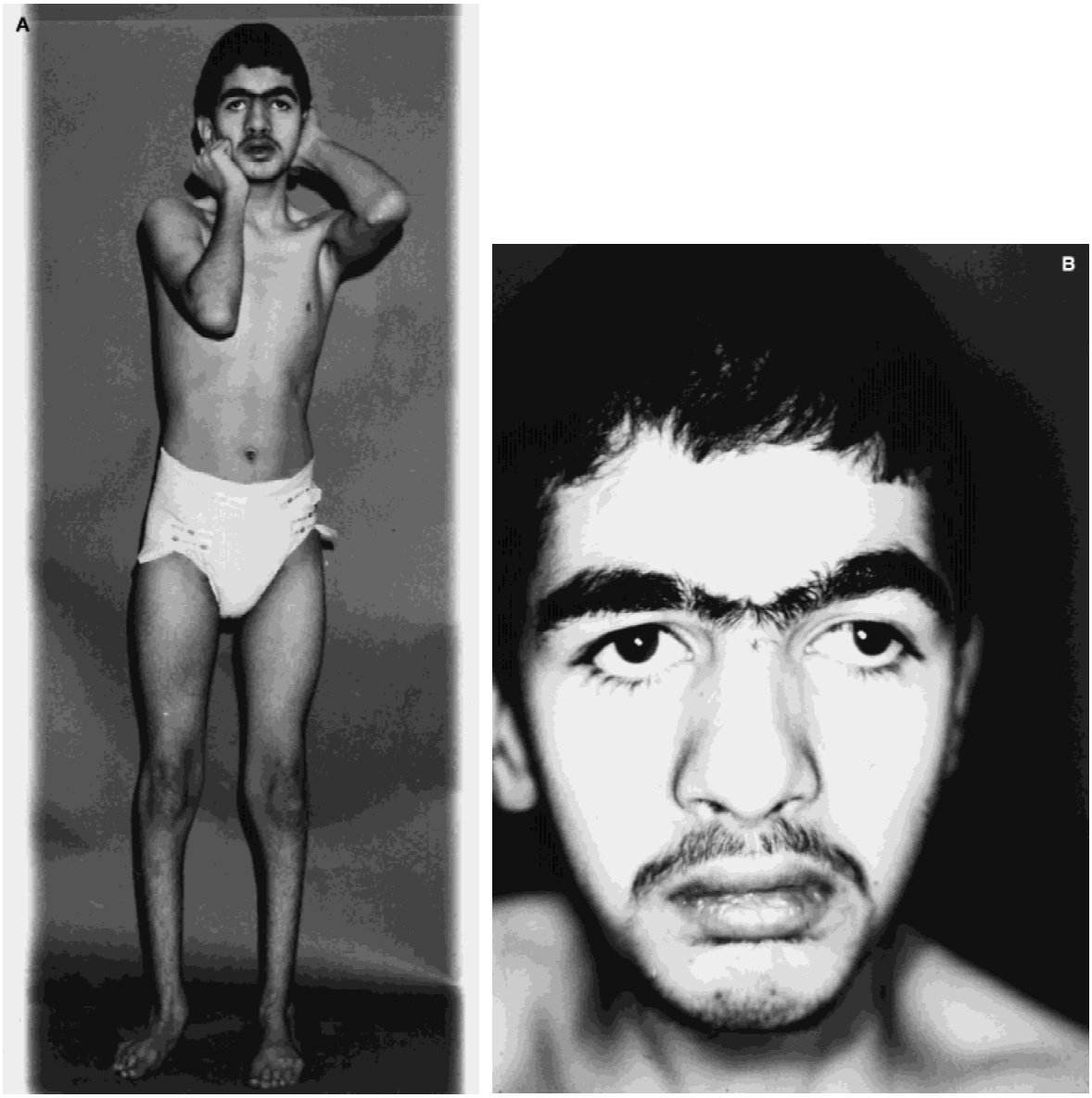

Fig. 2. **a:** Patient 1 at 17 years old; note poor muscle development in this slender patient. **b:** Facial appearance of patient 1: note downward slant of palpebral fissures and synophrys. **c:** Patient 3 at 4 years old: mild obesity and hypoplastic nipples. **d:** Frontal view of patient 3 at 4 years old, showing synophrys, simple philtrum, thin upper lip and small mouth.

disease gene (Fig. 3). The maximum two-point LOD score was found for the marker at D8S267 ($Z_{max} = 3.237$ at $O_{max} = 0.00$) as shown in Table I.

The 8q21.3-22.1 gene region harbors various possible candidate genes, e.g., the gene for syndecan 2, a membrane glycoprotein, especially expressed in neuronal synapses. Syndecan 2 belongs to the group of cell membrane receptors and is involved in mediating growth factor signals into the cell [Hsueh et al., 1998; Roskams et al., 1995]. A mutation within this gene could cause the phenotype described here and its pathogenetic role is considered as well in COH1 [Kolehmainen et al., 1997]. A further detailed EST search will be performed within these 26.8 cM, especially for those transcripts expressed in neuronal tissue or retina potentially involved in the phenotype of these patients.

DISCUSSION

We have studied two brothers and their affected first cousin with progressive microcephaly, mental retardation, short stature, and tapetoretinal degeneration. The severity of clinical symptoms varied among these closely related patients. Mental retardation varied from moderate to severe, microcephaly from −3.0 to −4.8 SD, and short stature from −2.8 SD to −4.2 SD; mild truncal obesity was described in two of them, while the other was very slender (Table II). Homozygosity mapping in this consanguineous family assigned the gene for this syndrome to a 26.8-cM region between the flanking markers D8S270 and D8S514 at 8q21.3 (Fig. 3). The putative gene region for the syndrome in these patients overlaps the locus for Cohen syndrome,

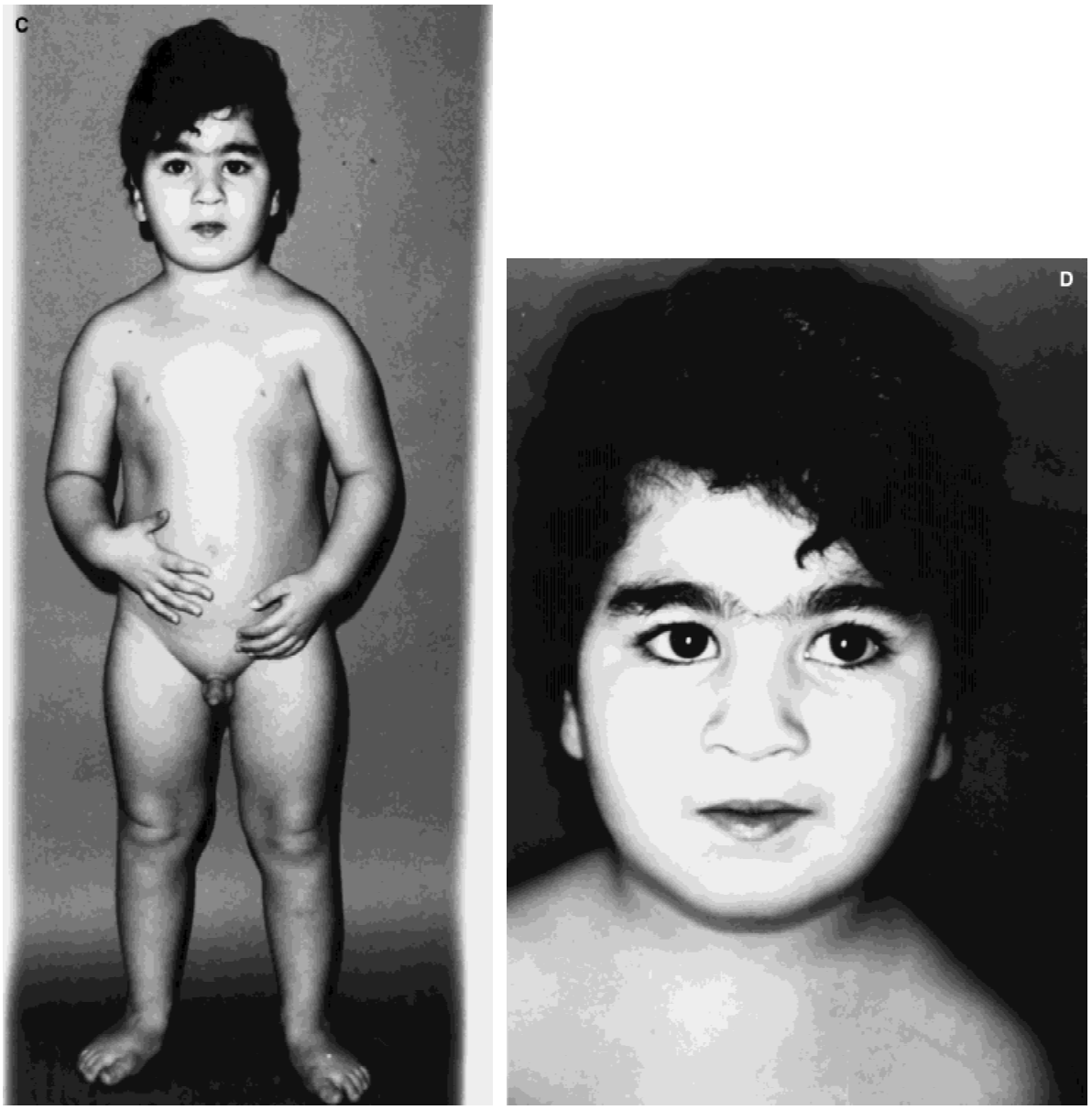

Fig. 2. (*Continued*).

which spans 10 cM between the flanking markers D8S270 and D8S521 [Kolehmainen et al., 1997]. The result of our linkage analysis focuses the nosologic discussion on Cohen syndrome as another form of microcephaly, mental retardation, and short stature. Several reports on Cohen syndrome describe different, often contradictory, clinical findings in affected patients. However, in brief, Cohen syndrome seems to comprise mild to severe mental retardation, normal to short stature, macrocephaly to severe microcephaly, the presence or absence of truncal obesity, and the presence of minor craniofacial anomalies.

We compared the phenotype of our patients with that of the well-characterized group of Finnish patients (Table II). They represent one of the biggest and most clinically homogeneous group of Cohen syndrome cases with known linkage status, which assigned the *COH1* gene to the overlapping region at 8q21.3 (Fig. 3). Furthermore, the haplotype analysis in Finnish families suggested the existence of one main mutation and possibly one or two rare ones, which could explain the uniform clinical picture in these patients.

Cohen syndrome in Finnish patients comprises psychomotor retardation, microcephaly, congenital hypotonia, and typical craniofacial anomalies. Micrognathia, short upper lip, flat philtrum, and prominent and broad upper central incisors together with open mouth constitute the typical facial phenotype. Except for microcephaly, these minor anomalies are difficult to recognize during the first years of life. Micrognathia often disappears with age. The appearance of the ocular region is considered to be important in establishing the

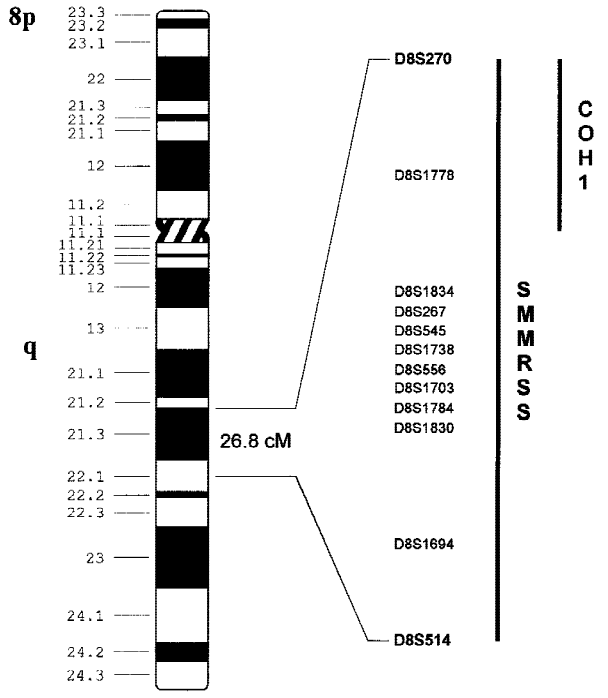

Fig. 3. Chromosomal localization of the gene region. The 26.8-cM interval on chromosome 8q21.3-22.1 is determined by flanking markers at D8S270 and D8S514. SMMRSS stands for syndrome of microcephaly, mental retardation and short stature. The shorter line corresponds to the 10-cM COH1 locus.

diagnosis of Cohen syndrome on the basis of a wave-shaped or flame-shaped lid opening, thick eyebrows, particularly in the lateral part, and long eyelashes [Norio et al., 1984]. A high nasal bridge and a low hairline are often described.

In our opinion, our patients do not have the typical facial appearance of the Finnish Cohen syndrome cases (Figs. 2b,d). Microcephaly from –3 to –5 SD is the only craniofacial manifestation common to both groups of patients. Eye findings in Finnish patients are highly variable and include myopia (varying from –1.5 to 17 D), tapetoretinal degeneration, astigmatism, and strabismus [Norio et al., 1984]. Optic discs are pale, retinal vessels narrow, and there is a bull's eye appearance of the macula and pigment deposits of the so-called bone cell type in the periphery. Tapetoretinal degeneration was found in patients 1 and 3 and was suspected in patient 2.

Persistent muscular hypotonia results in a marked delay of motor development in Finnish patients: they sat without support at 9 to 16 months and walked independently at 22 to 60 months [Norio et al., 1984]. Our patients were also markedly hypotonic. Motor development was more delayed in two patients than in the Finnish patients. These two patients did not learn to communicate verbally, in contrast to Finnish patients, who all had words or spoke in sentences. A cheerful disposition is described in all of the Finnish patients, while two of our cases had autistic symptoms.

Low-normal growth parameters were observed at birth in our and the Finnish patients. Progression of short stature with a severely retarded height in the oldest patient (–4.2 SD) was noted in our study, whereas postnatal growth was either normal or moderately retarded in Finnish patients, with a mean height standard deviation score of –2 [Kivitie-Kallio et al., 1999]. In contrast to prior reports, mild truncal obesity was seen only in 4 of 22 Finnish patients [Kivitie-Kallio et al., 1999]. The truncal obesity was obvious in our patient 2 and rather mild in patient 3. The oldest patient showed extremely poor muscle and fat tissue (Fig. 2a).

Intermittent neutropenia appears at an early age and is often associated with normal white blood cell count in Finnish patients [Kivitie-Kallio et al., 1997]. This neutropenia is presumed to be of bone marrow origin and accounts for repeated gingival or skin infections [Kivitie-Kallio et al., 1997]. Neutropenia associated with a normal white blood cell count as an important diagnostic sign of Cohen syndrome is not present in our patients.

The patients described by Mirhosseini et al. [1972] had additional anomalies such as long and slender fingers and toes, hyperextensible joints, moderately short stature, and lack of sexual maturation in one of the brothers. The affected individuals were severely retarded and could not speak. Although truncal obesity

TABLE I. Two-Point LOD Scores at Various Recombination Fractions for Markers on 8q21.3 and 8q22.1

Marker	Position (cM)[a]	LOD Score at Recombination Fraction of									Maximum recombination fraction	Maximum LOD score[b]
		0,000	0,001	0,010	0,050	0,100	0,150	0,200	0,300	0,400		
D8S270	102,1	–99.999	–0,971	0,001	0,574	0,714	0,724	0,68	0,514	0,285	0,129	0,728
D8S1778	108,8	2,073	2,069	2,030	1,859	1,643	1,424	1,21	0,776	0,375	0,000	2,073
D8S1834	116,3	1,876	1,674	1,641	1,498	1,317	1,129	0,93	0,524	0,178	0,000	1,998
D8S267	116,3	3,237	3,231	3,179	2,942	2,634	2,314	1,98	1,292	0,609	0,000	3,237
D8S545	116,3	1,678	1,674	1,641	1,498	1,317	1,129	0,93	0,524	0,178	0,000	1,678
D8S1738	116,8	2,634	2,630	2,590	2,407	2,170	1,925	1,672	1,142	0,584	0,000	2,634
D8S556	116,8	3,185	3,179	3,125	2,881	2,563	2,230	1,88	1,159	0,462	0,000	3,185
D8S1703	116,8	2,635	2,630	2,590	2,407	2,170	1,925	1,67	1,142	0,584	0,000	2,635
D8S1784	116,8	3,154	3,148	3,097	2,865	2,563	2,249	1,92	1,247	0,578	0,000	3,154
D8S1830	117,9	1,914	1,910	1,873	1,705	1,496	1,285	1,08	0,669	0,300	0,000	1,914
D8S1694	124,2	1,174	1,172	1,154	1,072	0,962	0,844	0,719	0,457	0,204	0,000	1,174
D8S514	128,9	–99.999	0,294	1,239	1,693	1,686	1,552	1,37	0,928	0,457	0,070	1,716

[a]Position of the marker on the genetic map according to Dib et al. [1996].
[b]The maximum LOD Score was obtained at the locus D8S267 at recombination fraction $\Theta = 0.00$.

TABLE II. Comparison of Clinical Characteristics in Our Patients and Reported Cases of Cohen and Mirhosseini-Holmes-Walton Syndromes

Clinical findings		Escobar [1990] (%)	Norio et al. [1984], Kivite-Kalio et al. [1999] (%)	Mirhosseini et al. [1972][a]	Mendez et al. [1985][a]	Steinlein et al. [1991][a]	This Study[a]
Growth and development	Mental retardation	82	100	2/2	2/2	2/2	3/3
	Obesity	90	18	1/2	0/2	2/2	2/3
	Short stature	82	32	1/2	2/2	1/2	3/3
	Hypotonia	90	100	0/2	0/2	2/2	3/3
Craniofacial anomalies	Microcephaly	65	100	2/2	2/2	2/2	3/3
	Short philtrum	90	100	n.a.	2/2	2/2	0/3
	Prominent upper incisors	62	100	n.a.	0/2	2/2	0/3
	Thick eyebrows	n.a.	100	n.a.	n.a.	n.a.	0/3
	Micrognathia	100	n.a.	n.a.	n.a.	n.a.	0/3
	High arched palate	90	n.a.	n.a.	2/2	n.a.	0/3
	Maxillar hypoplasia	82	n.a.	n.a.	n.a.	n.a.	0/3
Others	Chorioretinal dysplasia	rare	100	2/2	2/2	2/2	3/3
	Myopia	n.a.	83	n.a.	n.a.	x[b]	2/3
	Narrow hands/feet	90	100	2/2	2/2	2/2	3/3
	Neutropenia	19	100	n.a.	n.a.	2/2	0/3

Note: n.a. = data not available to us (in case of Finnish patients, the craniofacial signs were not considered significant and objectively measurable).
[a]Number patients who have the particular clinical finding.
[b]x = the lens enucleated early in the life of the patient.

was not mentioned in the text, it is present in patient 2 on one of the illustrations. Mendez et al. [1985] reported similarly affected sisters and designated the condition as Mirhosseini-Holmes-Walton syndrome. In 1986 Norio and Raitta concluded that the sibs reported by Mendez et al. [1985] probably had Cohen syndrome. Steinlein et al. [1991] also discussed the similarity between Cohen syndrome and Mirhosseini-Holmes-Walton syndrome and reported two brothers with manifestations of both syndromes.

Based on the diagnostic criteria for Cohen syndrome of Escobar [1990], the diagnosis of Cohen syndrome can be made in four of six reported cases of Mirhosseini-Holmes-Walton syndrome and our patients (Table II). The clinical appearance of most of the Finnish patients does not fit these diagnostic criteria since they do not exhibit the five major findings required by Escobar for a diagnosis of Cohen syndrome.

The above discussed data suggest that Cohen syndrome is a single but clinically very variable condition characterized by several nonspecific manifestations. We propose that the major criteria for Cohen syndrome should include mental retardation, short stature, hypotonia, microcephaly, chorioretinal dystrophy, and narrow hands and feet. Other clinical signs such as truncal obesity, neutropenia, myopia, and minor facial anomalies of short philtrum, prominent upper incisors, thick eyebrows, micrognathia, high arched palate, and maxillary hypoplasia, represent minor diagnostic criteria and increase the probability of Cohen syndrome (Table II). To establish the diagnosis of Cohen syndrome the patient should present with at least three of the major signs and at least one minor sign.

The remarkable similarity of the chromosomal localization of COH1 and the condition in our patients suggests that these two clinically similar conditions are allelic. The existing differences in the phenotype could be attributed to different mutations within the same gene causing this genetic disease or to a different genetic background in patients originating from such different populations. Nevertheless, the result of homozygosity mapping in the described family does not exclude the existence of a different gene in the vicinity of the COH1 locus causing a similar genetic condition. Our hypothesis—that the syndrome described here, Mirhosseini-Holmes-Walton, and Cohen syndrome are allelic—can be tested after the characterization of the *COH1* gene and the mutations accounting for the Cohen syndrome phenotype.

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